

### REMARKS

Claims 1-16 and 18-30 are pending in this application, as previously amended by the Applicants in a Preliminary Amendment filed March 13, 2002. Applicants have amended the specification and claims 1 and 9-11 in order to correct certain inaccuracies and typographical errors.

In the September 2, 2003 Office Action, the Examiner rejected claims 1, 2, 6-8, 10-12 and 14-16, apparently under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, in claim 1, it is unclear as to how D, methotrexate, is combined into Formula I, and the term “phospholipid head group” is not understood. (Applicants note that, in accordance with the Examiner’s suggestion, claim 2 has been canceled, and incorporated into claim 1.) Applicants traverse the Examiner’s rejections, as discussed below.

With regard to the attachment of D, methotrexate, into Formula I, it is clear from the instant specification that methotrexate may be linked to the phospholipid moiety at any of the possible attachment sites of methotrexate, as would be recognized by a person skilled in the art. For example, the specification exemplifies the two carboxylic acid groups of methotrexate,  $\alpha$  and  $\gamma$ , as preferred sites for attachment (see Example 1 at page 16 and Example 4 at page 29). Furthermore, as is well known to one of ordinary skill in the art, methotrexate may also be linked through any of its amino groups. Especially in view of the disclosures of the specification, one of ordinary skill in the art would readily understand how methotrexate is combined into Formula I of claim 1.

Applicants also point out that the term “phospholipid head group” in R2 of claims 1 is well-known in the art. Specifically, it is well understood from basic biochemistry that phospholipid molecules are made up of a hydrophilic polar head group containing one or more phosphate groups and a hydrophobic tail made up of two fatty acyl chains. See, e.g., Stryer, Biochemistry, 2<sup>nd</sup> Edition, W.H. Freeman and Company, 1981, page 211. The head group has a region that may vary among various phospholipids, and the lipophilicity of the entire lipid molecule is effected by the nature of the phospholipids group, as discussed in the specification at page 10, lines 7-11. Applicant believes that one of ordinary skill in the art of phospholipids

would have a basic understanding of biochemistry that includes the structures of phospholipids. Thus, it is clear that the term “phospholipid head group” in claim 1 is well known to those of ordinary skill in the art, is discussed in the specification and needs no further explanation.

Accordingly, these rejections of claim 1 for being indefinite should be withdrawn.

The Examiner stated that claims 2-5 stand withdrawn, pending clarification, because claim 1 “is too burdensome to examine without specifying the variables.” Applicants believe that they have sufficiently clarified the variables above. Applicants have canceled claim 2 and have incorporated its limitations into claim 1, and have withdrawn claim 3 as being drawn to non-elected subject matter. Claims 4 and 5, however, are dependent upon claim 1, whose variables have been sufficiently specified by Applicants above, and Applicants respectfully request that examination of claims 4 and 5 proceed.

The Examiner stated that claim 9 stands withdrawn as being drawn to non-elected subject matter. In response, Applicants respectfully point out to the Examiner that only the last element recited therein, which includes the fluorodeoxyuridine residue, refers to non-elected subject matter. Accordingly, Applicants have amended claim 9 to delete the last compound, which is a non-elected anti-proliferative drug, leaving only compounds directed to methotrexate. Thus, the withdrawal of claim 9 should be reversed, and claim 9 should be rejoined into the application and allowed.

The Examiner also objected to claims 10 and 11 on the basis that “their exact chemical structure is unclear”, and the Examiner requested that the chemical structures be provided. Applicants disagree with the Examiner’s assertion and traverse the objections. Applicants assert that the chemical structures of the molecules named in claims 10 and 11 are clearly and unambiguously provided by, and are known by simply looking at, the chemical names of those structures. Applicants believe that one of ordinary skill in the art of phospholipids would have a basic understanding of biochemistry that includes knowledge and understanding of the structures specifically named in claims 10 and 11.

However, Applicants contend that, even without this understanding, one of ordinary skill in the art would find the structures of the molecules of both claims 10 and 11 to be fully explicated in the instant specification, as amended. Specifically, the molecule of claim 10, 1-stearoyl-2-[3- $[\alpha$ -MTX amido)-propanoyl]-sn-glycero-3-phosphocholine, is identified on page 23 as being  $C_{49}H_{79}N_{10}O_{12}P.HCl3H_2O$ . The molecule of claim 11, 1-stearoyl-2-[3-( $\alpha$ -dodecylate- $\gamma$ -MTX-amido)-propanoyl]-sn-glycero-3-phosphocholine, is identified on page 24 as  $C_{61}H_{103}N_{10}O_{12}P.3H_2O$ . From this information, one of ordinary skill in the art would know, for example, that the R1 group of the molecule of claim 10 or 11 is a stearyl moiety and that the phospholipid moiety of R2 is phosphocholine.

The instant specification provides additional guidance with respect to the specific components of said compounds in claims 10 and 11, as follows:

- the R1 group is described on page 10, lines 3-6 of the specification as: “In preferred embodiments of the invention, R1 is an alkyl residue of an odd number of atoms. More preferably, R1 is an alkyl residue of 15 or 17 carbon atoms, yielding, respectively, the naturally occurring palmitoyl ( $C_{16}$ ) or stearyl ( $C_{18}$ ) residues at the sn-1 position of the phospholipids.” (Emphasis added)

- the R2 group is described on page 10, lines 7-11 of the specification (as amended) as: “The lipophilicity of the lipid molecule is also affected by the nature of the phospholipids head group, denoted as R2 in the prodrug of the general formula I. The phospholipids moiety may be selected from, but is not limited to, the group consisting of phosphatidic acid, phosphocholine, phosphatidylethanolamine, phosphatidylinositol, and phosphatidylserine.”

- the Z component of the bridging group  $-C(O)-Z-X$  is described, for example, on page 11, lines 21-24 of the specification as: “Component Z of the bridging group may be a saturated or unsaturated, straight-chain or branched, substituted or unsubstituted hydrocarbon chain having from 2 to 15 carbon atoms, which may include cyclic elements and is optionally interrupted by one or more atoms selected from oxygen and sulfur atoms.” In the compounds disclosed in claims 10 and 11, Z is propanoyl.

- X is described on page 10, lines 28-30 of the specification as: “Preferably the appropriate drugs are linked to the bridging group through a carboxyl, oxy, amine or mercapto group, thus generating an ester, amido or a thio bond”. (Emphasis added).

- D is described on page 10, lines 17-23 of the specification, with respect to the compound of claim 10 as: "In a preferred embodiment, binding of the drug to the lipid-bridge moiety is specifically directed to the  $\alpha$ -carboxylic group of the methotrexate (herein denoted  $\alpha$ -MTX)", and with respect to the compound of claim 11, "In another preferred embodiment, the methotrexate moiety is linked to the phospholipids through the  $\gamma$ -carboxyl of methotrexate (herein denoted  $\gamma$ -MTX)."

Even further, albeit unnecessary, guidance with respect to the specific components of said compounds in claims 10 and 11 comes from the fact that claims 10 and 11 are both dependent on claim 1, which provides the overall chemical structure for the prodrugs of the instant invention. Claim 1 recites a prodrug of a general formula I, wherein an R1 group is a saturated or unsaturated, straight-chain or branched, substituted or unsubstituted hydrocarbon chain having from 2 to 30 carbon atoms, a moiety Z is a saturated or unsaturated, straight-chain or branched, substituted or unsubstituted hydrocarbon chain having from 2 to 15 carbon atoms, which may include cyclic elements and is optionally interrupted by one or more atoms selected from oxygen and sulfur atoms, a direct covalent bond X, or, alternatively, an O, S, NH, or C(O) group joins Z to a moiety D, which is methotrexate or pharmaceutically acceptable derivatives thereof, and an R2 moiety is H or a phospholipid head group (further defined in claim 8 as being selected from the group consisting of choline, ethanolamine, inositol and serine).

Accordingly, Applicants assert that the chemical structures of the molecules named in claims 10 and 11 are clearly and unambiguously provided for in the application and would be known to one of ordinary skill in the art, and Applicants respectfully request that the objections to claims 10 and 11 be withdrawn.

The Examiner stated that claim 13 stands withdrawn as being drawn to non-elected subject matter. Applicants respectfully point out to the Examiner that he has already stated in the Office Action dated June 30, 2003 that claim 12, which claims pharmaceutical composition comprising a prodrug of the general formula I according to claim 1 as an active ingredient and a pharmaceutically acceptable carrier, will be examined with the specific drug of claim 1. Claim 13 adds to claim 12 only an additional neoplastic agent. The Examiner contends that this

additional active ingredient makes claim 13 of different scope than claim 12, and it must therefore be classified in a different search area and searched and examined separately.

However, contrary to the Examiner's statements, according to Patent Cooperation Treaty (Rule 13.2) and U.S. Patent and Trademark Office law, this difference in claim scope is irrelevant. Unity of invention is not lost due to the presence of an additional active ingredient, so long as the same special technical feature is present, i.e., the pro-drug of general formula I as described in claim 1, which the Examiner must concede is the case. As set forth in M.P.E.P. § 1850, if the independent claims avoid the prior art and satisfy the requirement of unity of invention, there is no lack of unity of invention for claims that depend from the independent claims. Moreover, the M.P.E.P. explicitly states that "it does not matter if a dependent claim itself contains a further invention." This appears to be the case regardless of whether the further invention or element is separately classified. It is axiomatic that, if the invention of claim 12 is patentable, then any claims dependent upon it will also be patentable, regardless of whether the additional element is to be classified and searched separately. There is thus no need for further searching to determine if claim 13 is patentable, since there can be no detracting from the patentable features of claim 12 by the additional element in claim 13. If the composition claimed in claim 12 is novel, the composition claimed in dependent claim 13 is also novel, regardless of the identity of the additional component. Accordingly, it is clear that the presence of an additional active ingredient in claim 13, and the resulting difference in claim scope, does not result in loss of unity of invention. Applicants respectfully request that the Examiner rejoin claim 13 into the application and allow it to issue.

Further, the Examiner appears to reject Applicants' election of the method of use in claims 23-29 under 35 U.S.C. § 112, first paragraph (treatment of uncontrolled cell growth), and instead recommends election of the method of use in claims 18-19 (treatment of an inflammatory condition). Specifically, the Examiner contends that "[t]reating controlled [sic] cell growth would be very difficult to prove, and not acceptable on its [sic] face under 35 USC 112, 1<sup>st</sup> paragraph." The Examiner further asserts that under the rules governing 371 applications, "37 CFR 1.475 makes it clear that applicant [sic] may have one use of their compounds examined with the elected compounds. Applicants have not amended their method claims to one, therefore

they stand withdrawn.” The Examiner has therefore withdrawn all of claims 18-29. Applicants traverse these rejections.

With regard to which method of use is elected, Applicants thank the Examiner for his suggestion as to the most establishable and believable utility to be elected. However, in the Response to Office Action dated July 30, 2003, in view of the fact that claims 18-29 allege more than one use, Applicants specifically elected the method of use in claims 23-29, namely a method of treating uncontrolled (not controlled, as stated by the Examiner) cell growth, and Applicants choose not to change this election at this point.

Moreover, Applicants do not agree with the Examiner that treating uncontrolled cell growth would be very difficult to prove. On the contrary, regarding the issue of support for the method of use elected, treatment of diseases such as cancer that are characterized by uncontrolled cell growth, Applicants point out that ample support is provided in the instant specification for the use of the claimed compounds in inhibiting cell growth of human leukemia and rat glioma cells. See, for example, Example 4, which serves to sufficiently demonstrate the utility of these compounds for the treatment of pathological conditions characterized by uncontrolled cell growth. Accordingly, it is clear that the specification provides sufficient support for use of the compound of Formula I in claim 1 for treatment of diseases related to uncontrolled neoplastic and other cell growth.

With respect to Applicants not having not amended their method claims to one and the Examiner’s withdrawal of all claims 23-29, Applicants state that there is no requirement for the elected method of use to be reduced to only one claim. The Examiner’s attention is directed to the PCT Gazette, Special Issue of 30 August 2001, Administrative Instructions Under the PCT, in the discussion regarding unity of invention, wherein it is noted that:

The method for determining unity of invention under Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application: (i) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product ....

Accordingly, contrary to the Examiner's position, Applicants are not limited to only one method of use claim. In accordance with the PCT Rule 13.2 and 37 C.F.R. § 1.475, Applicants are limited to only one independent claim, but no restriction is placed on the number of dependent claims therefrom. Therefore, Applicants respectfully request that the Examiner rejoin claims 23-29 into the application and allow them to issue.

With regard to whether Applicants have chosen one specific disease from among those listed in claim 29, Applicants argue that whether or not Applicants have made such a choice is no reason to withdraw claims 23-28 because claims 23-28 do not depend from claim 29. In fact, Applicants argue that the requirement or need for Applicants to choose one specific disease from claim 29 is overly restrictive. As shown in the specification, various DP-methotrexate compounds of the invention have been shown to be effective in inhibition of several different tumor cell lines. Applicants respectfully request that the Examiner rejoin claims 23-28 and 29, and examine claim 29 along with claims 23-28.

Finally, the Examiner states that Applicants may not also elect claim 30, as that would be two methods, and the Examiner appears to reject claim 30 under 35 U.S.C. § 103, as obvious over "any of the art of record" because it is notoriously old and known since the time of Alchemists working in caves. Applicants traverse these rejections.

With regard to the Examiner's disallowance of Applicants' election of claim 30 because that would be two methods, Applicants again point out to the Examiner that PCT Rule 13.2 and 37 C.F.R. § 1.475 allow an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product to be within the same application. In fact, the Examiner stated as much in the June 30, 2003 Office Action. Claim 30, which is an independent claim for a process for the manufacture of the product, is specifically permitted in this application under these rules and should not be withdrawn from the application. Accordingly, this rejection should be withdrawn.

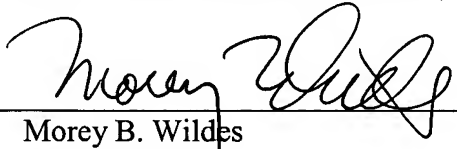
With regard to the Examiner's rejection of claim 30 because it "is notoriously old and known since the time of Alchemists working in caves", Applicants argue that, if the composition in claim 1 is novel, then the method of making said composition is novel as well. To follow the Examiner's logic would be to invalidate all methods of making compositions, since, as the Examiner contends, "the making of a composition ... is notoriously old and known since the time of Alchemists working in caves." Accordingly, this rejection should be withdrawn

### **Conclusion**

Reconsideration of the present application, as amended, is requested. It is respectfully submitted that claims 1, 4-16 and 23-30 remaining in this application are patentable. If, upon review, the Examiner is unable to issue an immediate Notice of Allowance, the Examiner is respectfully requested to telephone Applicants' undersigned attorney in order to resolve any outstanding issues and advance the prosecution of the case.

An early and favorable action on the merits is earnestly solicited.

Respectfully Submitted,  
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